Practice research in the field of gout - clinical pharmacology of antihyperuricemic drugs

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Chapter 2

Management of gout

Chapter 2.1

Gout in clinical practice

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Abstract

Gout is characterised by the formation and deposition of monosodium urate (MSU) crystals attributable to the metabolism of purines or uric acid. The disease is associated with recurrent episodes of acute joint pain caused by the deposition of MSU crystals in the joints. As well as affecting the joints, skin/subcutaneous tissue and kidneys are also affected by tophaceous deposits, cellulitis, urate nephropathy and kidney stones, respectively. In most cases the cause of gout is not easily identifiable, but there are a number of factors that could contribute to increases in urate (uric acid) levels, such as renal function disorders, obesity, and use of diuretics. Primary gout tends to involve low uric acid excretion, the cause of which originates primarily in the proximal tubulus. Only a minority of gout cases involve overproduction of uric acid.

There are several classes of drugs available for the treatment of gout. These include anti-inflammatory drugs (glucocorticosteroids, colchicine, and non-steroidal anti-inflammatory drugs), and antihyperuricemic drugs (allopurinol, benzbromarone, probenecid, and the novel urate-lowering drug febuxostat, which is currently under review by the EMEA). In addition, lifestyle changes can also help to prevent the occurrence of gout or reduce the likelihood of recurrent disease. This review summarises the use of these drugs in the prevention and treatment of the disease, applies data from current recommendations, and provides an overview for clinical practice.

Introduction to gout

Gout is the collective name for several disorders that are characterised by the formation and deposition of monosodium urate (MSUr) crystals [1]. The condition is associated with recurrent episodes of acute joint pain due to the deposition of MSUr crystals in the joints. In addition to the effects observed in the joints, skin/subcutaneous tissue and kidneys are also affected by tophaceous deposits, cellulitis, urate nephropathy and kidney stones, respectively. In most cases, no identifiable underlying cause of gout is present, but evident factors are usually present that could contribute to increases in urate (uric acid) levels, such as renal function disorders, obesity, and the use of thiazide diuretics.

The annual incidence of gout is 0.1% in men with serum urate (sUr) <0.42 mmol/l (7.1 mg/dL) rising to 7.0% in those with sUr >0.60 mmol/l (10.1 mg/dL). The condition is less common at sUr levels <0.35 mmol/l (5.9 mg/dL), but regularly occurs at levels >0.55 mmol/l (9.3 mg/dL). In 2006, the European League against Rheumatism (EULAR) released recommendations for the diagnosis and treatment of gout [2-3].

Gout pathophysiology

Uric acid is formed from nucleic acid either endogenously from cell breakdown or exogenously from metabolism of food. The solubility of MSUr is reduced by cooling and acidification of the microenvironment, which can result in acute formation of urate crystals. One-third of urate is excreted by the gut and two-thirds are excreted renally. In the kidney, uric acid is mainly filtered in the glomerulus and then almost entirely reabsorbed in the proximal tubulus by the urate anion transporter 1 (URAT-1). Finally, 75% of uric acid is excreted by the distal tubulus. Some drugs, such as cyclosporine A and diuretics, can inhibit this excretion. Excessive consumption of alcohol (particularly beer), sweetened soft drinks, fructose, meat, and seafood can also increase levels of sUr [4].

Uric acid is reabsorbed via the URAT-1 by utilisation of lactate, pyruvate or other compounds. Inhibition of URAT-1 can be achieved by uricosurics, and endogenous production can be inhibited using xanthine oxidase inhibitors (XOi), such as allopurinol. Febuxostat may become the alternative XOi, as it is currently under review by the EMEA. Uric acid deposits can also be lysed by the enzyme uricase, the gene for which is defective in humans because of an evolutionary mutation. The combined absence of uricase and almost total reabsorption of filtered urate, explains that humans have 10-fold higher sUr levels than other mammals.

Characteristics of gout presentation

Before gout can be diagnosed, it must be established whether the symptoms are caused by disrupted uric acid metabolism (chronic gout), and/or tophaceous deposits of MSUr crystals (micro-tophi) in joints, and other tissues that are observed during acute attacks of gout. The

clinical practitioner can confirm the presence and type of crystals by polarisation microscopy [1, 5-6].

The characteristic profile of gout is that of severe monoarthritis occurring within several hours. The first metatarsophalangeal joint is affected in 50% of gout attacks, and this is known as podagra. Gout may be localised in other joints, but shoulders, hips and the vertebral column are rarely affected. The initial gout attack usually involves monoarthritis, but long-term gout over several years may become polyarticular and could lead to increasing joint damage. Similarly, a positive uric acid balance over a number of years can cause tophaceous deposits, possibly with periodic arthritis.

Urate production

Primary gout tends to involve low urate excretion, which is primarily originated in the proximal tubulus. Only a minority of cases involve overproduction of urate. In some treatments of cancer (particularly lymphomas and leukemias), patients can develop tumour lysis syndrome including severe hyperuricemia with risk of urate nephropathy. By definition, overproducers of urate excrete >6.0 mmol/l (1 g) in urine per 24 hours on a normal diet, or >3.6 mmol (600 mg) per 24 hours after five days on a low-purine diet. Patients have a low excretion of urate when less than half of the threshold value is present in a 24-hour urine sample, and the combination of low excretion with hyperuricemia lies between the threshold values (without a low-purine diet: 3-6 mmol/24 hours). Based on clinical observations, the author recommends that the patient's urate excretion status should be taken into account for choice of antihyperuricemic drug. However, no evidence for this approach is available in the literature.

Urate nephropathy in gout

Aggressive chemotherapy among patients with chronic leukemia or malignant lymphoma could cause an excessive supply of uric acid resulting in acute urate nephropathy due to the deposition of sodium urate crystals in collection ducts and ureters.

In chronic hyperuricemia, the risk of developing renal calculi increases as serum urate concentrations rise. The risk is about 10% with serum urate 0.42-0.48 mmol/l, but can rise to 50% with serum urate concentrations >0.70 mmol/l. In the absence of stones or other risk factors (such as hypertension), the risk of urate nephropathy has generally been considered low [7].

Radiographic presentations of gout

X-ray examination at the initial onset of gout has revealed no abnormalities except for possible pre-existing arthrosis and soft tissue edema. Cartilage and bone might be affected by chronic and/or recurring arthritis, and subsequently exhibit narrowing of the joint cavity because of the disappearance of cartilage, and erosions or cysts because of contact with juxta-articular bone. These abnormalities and the appearance of the erosions may raise suspicions of gout, but

erosions are a secondary manifestation and non-diagnostic characteristic of gout. These variations in the presentations of gout mean that treatment should be tailored accordingly (Table 1).

Table 1. Therapeutic indications and treatment regimens

Indication	Regimen		
	Anti-inflammatory treatment	Prevention [1]	Antihyperuricemic treatment
1. Asymptomatic			
(a) no history	-	-	-
(b) suspected history	-	- [2]	-
2. Crystal-induced gouty arthritis			
(a) frequency of attacks <2 per annum	+	- / +	-
(b) frequency of attacks >2 per annum	+	+	+
3. Tophaceous gout	-	+	+
4. Radiographic lesions due to gout/tophi	-	+	+

[1] Lifestyle changes and elimination of hyperuricemic factors in secondary gout.

[2] Only upon evidence of crystal formation, e.g. swelling.

Treatment strategies for gout

Several approaches to the treatment of gout are available depending on the patient's presentation of the disease. Optimal treatment often requires a combination of pharmacological intervention and lifestyle changes. Treatment should be tailored to the patient's specific risk factors (high sUr, previous attacks and radiographic signs), the clinical phase of the disease (acute, recurrent, tophaceous) and general risk factors, such as obesity and alcohol consumption. Primary prevention of gout often involves changes in lifestyle, such as a low-purine/weight-reducing diet or restricting alcohol intake; however, many patients are unlikely to undertake such changes until they are diagnosed with the disease, which often occurs when the symptoms are presented in the form of an attack of gout. Acute gout is usually treated by reducing the inflammation of the affected joint with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids, and cooling. Once the acute gout has subsided the objective is to prevent disease recurrence. This might involve lifestyle changes and low doses of NSAIDs or colchicine. In patients with high sUr levels who suffer from frequent attacks of gout, the use of urate-lowering drugs is warranted. Antihyperuricemic drugs include XOi (such as allopurinol), which act by inhibiting uric acid production thereby reducing serum urate concentrations. Other antihyperuricemic therapies include uricosuric drugs, such as benz-bromarone and probenecid, which inhibit the reabsorption of uric acid mediated by URAT-1.

Table 2. Antihyperuricemic drugs in gout

Drug	Action: indication	Daily dose: standard
Allopurinol p.o.	XOi: all	100-900 mg: 300 mg
Benzbromarone p.o.	URAT-1: low excretor, subject to intolerance or allergy to allopurinol (as per p.i.l.)	50-200 mg: 100 mg
Febuxostat p.o.	XOi: all	80-120 mg: 80 mg
Probenecid p.o.	URAT-1: low excretor	500-2,000 mg: 1,000 mg
Sulphinpyrazone p.o.	URAT-1: low excretor	100-800 mg: 600 mg
Rasburicase i.v.	UrO: lytic effect on tophi	Compassionate use: e.g. 0.2 mg/kg in 60 min. infusion on day 1, then 1x per week; (+ methylprednisolone 100 mg i.v.)

Legend: i.v.: intravenous; p.i.l.: patient information leaflet; p.o.: oral; UrO: urate oxidase; URAT-1: urate anion transporter 1; XOi: xanthine oxidase inhibitor.

Table 3. Suggested strategy for initiation of antihyperuricemic therapy

1.	Confirmation of diagnosis: detect crystals by means of polarisation microscopy
2.	>2 gout flares per annum or tophi/joint destruction due to gout attacks
3.	Therapeutic advice [1]: allopurinol 100-300 mg/day [2]
4.	Laboratory monitoring of effectiveness at 6-8 weeks: [3] (a) sUr <0.30 mmol/l, then continue with this (b) sUr >0.30 mmol/l, but no further attacks (without colchicine/NSAID), then continue with this (c) sUr >0.36 mmol/l plus gout attacks and uUr >4.0 mmol/24 hours, go to 5 (d) sUr >0.36 mmol/l plus gout attacks/persistent tophi with uUr <4.0 mmol/24 hours, go to 6
5.	Therapeutic advice: increase allopurinol with 100 mg/day or double the dose [b]
6.	Therapeutic advice: add uricosuricum, e.g. benzbromarone 100 mg/day, or probenecid 1,000 mg/day
7.	Laboratory monitoring of effectiveness sUr and uUr (possibly, pH [4]) after 6 months: see 5
8.	N.B.: when trying to clear tophi, target value sUr <0.30 mmol/l

Legend: sUr: serum urate; uUr: 24-hour excretion of urate in urine; NSAID: non-steroidal anti-inflammatory drug.

1 Subject to motivation and tolerance by patient.

2 Subject to calculated creatinine clearance (cCC) >50 ml/min, if cCC <50 ml/min, then only increase allopurinol with 100 mg/day. Serum oxipurinol concentrations might be measured in patients with renal insufficiency.

3 Target value for sUr ≤0.36 mmol/l might be sufficient when there are no further gout attacks despite withdrawing colchicine/NSAID, otherwise lower target value of 0.30 mmol/l.

4 If experiencing kidney stones or uUr >6.0 mmol/24 hours and pH <7.0 consider alkalising with sodium bicarbonate.

The following is an overview of the different drug classes and their potential use as part of the treatment strategies for gout. Information on these drugs is presented in Table 2 and the current therapeutic strategy is summarised in Table 3.

Primary prevention of gout

Primary prevention of gout involves changes in lifestyle, such as changes to diet (low-purine/weight-reducing diet) and restricting alcohol consumption. No randomised studies have been conducted evaluating the effect of lifestyle changes on the incidence of attacks in patients with gout. Nevertheless, experts agree that lifestyle changes have some effect. Lifestyle advice is also given by physicians in daily practice when gout symptoms appear. However, fewer than 20% of patients with gout seeking medical advice are prepared to make long-term changes in lifestyle [8]. Recently, the negative role of meat, seafood and beer consumption, and the protective role of dairy products in the development of gout were demonstrated in a prospective study over a 12-year period among a population of around 47,000 healthy male subjects [9].

Reducing the symptoms of acute gout

Treatment of a gout attack involves reducing the symptoms of inflammation that are responsible for the pain associated with the condition. The following section outlines the treatment options available for acute gout.

Cooling

Some evidence from a small-scale controlled study indicates that local ice therapy could be of additional benefit in conjunction with a systemic treatment [10].

Corticosteroids

For many years, the evidence for treatment of acute gout with glucocorticosteroids was inconclusive [11]. Several open-label studies suggest efficacy of intra-articular injection of corticosteroids in major joints presenting with gout, which is in line with the author's observations in daily practice. The incidence of severe gouty attacks when using 7.5-15 mg prednisone daily among patients treated with cyclosporin A suggests that relatively high doses of corticosteroids (e.g. >40 mg prednisone/day) might be required to treat acute gout [12]. However, primary treatment of gout using systemic corticosteroids could be linked with rebound flares, therefore combination therapy of corticosteroid with colchicine is recommended [13].
Corticosteroids administered via intra-articular injection and by systemic administration should preferably used only temporarily because of their associated risk factors on glucose metabolism and the decalcification of bones. Presently, predniso(lo)ne is recommended at a dose of 10 mg once daily for 1 week, then 5 mg once daily until sUr is at target level (for a maximum of 3 weeks).

Recently, it was shown in a randomised controlled, double-blinded trial that oral predniso(lo)ne 35 mg per day and naproxen 500 mg twice daily were equally effective in the initial treatment of gouty arthritis over 4 days [14].

Colchicine

This alkaloid is prepared from autumn crocus (*Colchicum autumnale*). Colchicine has a high tissue distribution and tissue bond, and persists in the leukocyte for 10 days. It is excreted in bile (enterohepatic circulation) and urine. In the acute phase (first two days) of a gout attack, colchicine can powerfully reduce the symptoms of gout. Therefore, colchicine is often used as a first-line treatment for acute attacks of gout [3]. Currently, one placebo-controlled study is conducted in which 1 mg colchicine is initially administered followed by 0.5 mg every 2 hours until pain disappears or toxicity occurs. After 24 hours, there was a >50% reduction in pain in 42% of the patients in the colchicine group compared with 9% in the placebo group. After 48 hours, the percentages were 73% and 36%, respectively (p<0.05). However, in the colchicine group, all patients developed symptoms of toxicity (nausea, vomiting, or diarrhoea), most of which started within 24 hours of receiving the drug. Clinical improvement was observed in 41% of patients before the onset of toxicity [15]. Consequently, this colchicine programme was abandoned. In addition, in patients with renal/hepatic function disorders or among patients receiving substances inhibiting the CYP3A4 enzyme, such as erythromycin, verapamil and grapefruit juice, increased toxicity can occur following treatment with colchicine [16].

When administered at doses of 0.5 mg one- to four-times daily (maximum 0.5 mg six times daily), the drug inhibits the phagocytosis of crystals and has no direct effect on the metabolism of uric acid. The current dosing regimen is 0.5 mg four-times daily, then after 3 days 0.5 mg three-times daily, and then after 6 days 0.5 mg twice daily. This regimen is continued until the uric acid level has reached the ‘target’ concentration after the first attack, or as a means of reducing annual attacks in the absence of sUr-lowering therapy. In patients with a (calculated) creatinine clearance of <50 ml/min, dosage must be reduced to 0.5 mg/day. In the event of (pre)terminal renal insufficiency with a creatinine clearance of <10 ml/min, it is advisable to avoid colchicine to prevent toxicity and specific adverse events (AEs), such as myopathy and neuropathy [17]. Otherwise, a positive reaction of arthritis to colchicine might be mistaken as evidence of gout.

No controlled trials have been conducted to assess the prophylactic use of colchicine as a single agent; however, it has been shown to reduce the likelihood of recurrent gout for up to 6 months during the initiation of allopurinol treatment. As a preventative measure, colchicine is recommended at a dose of 0.5 mg once or twice daily, dosed in such a way as to avoid nausea or diarrhoea [18]. In this instance, NSAIDs are only indicated if colchicine monotherapy is inadequate, or when there are contra-indications for colchicine.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs are often the first choice for the treatment of acute gout. A placebo-controlled study of reasonable quality compared 30 mg/day tenoxicam with placebo in the treatment of gout [19]. After 24 hours, a reduction in pain of >50% was achieved in 67% in the tenoxicam group compared with 26% in the placebo group ($p<0.05$). However, after 4 days there was no longer any difference between the two groups. The effectiveness of different NSAIDs was compared in nine more studies. Two high-quality studies demonstrated equivalence for etoricoxib compared with indomethacin in the treatment of gout from days 2-5. Fewer drug-related adverse effects were found in the etoricoxib group [20-21].

Current dosing strategies for NSAIDs include indomethacin 50 mg three-times daily, naproxen 500 mg twice daily, ibuprofen 600 mg three-times daily, or diclofenac 50 mg three-times daily, and possibly etoricoxib 120 mg once daily for a maximum of 1 week.

Treatment options for prevention of recurrence of gout

When gout has subsided, it is important to reduce the sUr concentration to prevent recurrence of gouty attacks. This involves restriction of alcohol, weight-loss in cases of obesity (not too rapidly as this can trigger gout), and ensuring adequate diuresis. Dietary measures are very important: the risk of gout increases by extra consumption of meat, fish, and beer, but is reduced by dairy products [9]. However, a strict low-purine diet can achieve only a limited reduction in sUr levels (≤0.10 mmol/l or 1.7 mg/dl), and many patients have difficulty with adhering to long-term dietary changes [8]. If possible, it is recommended that patients should discontinue diuretics. However, the effectiveness of these measures is limited and is not supported by controlled studies.

With tophaceous or recurrent gout (>2 attacks per annum) the use of urate-lowering therapy may be warranted [22]. Achieving lower sUr, particularly <0.36 mmol/l (6.1 mg/dl), is associated with a reduced chance of recurrent gout attacks [23-24]. Achieving sUr levels of <0.30 mmol/l (5.0 mg/dl) in tophaceous gout might be associated with a faster disappearance of tophi [25-26]. In contrast, asymptomatic hyperuricemia requires no treatment. The maintenance dose of urate-lowering drugs is preferably adjusted to the clinical effect: (1) prevention of gout attacks without using colchicine and/or NSAIDs, (2) disappearance of tophi based on the sUr-concentration with tophaceous deposits.

It is plausible that for tophi to disappear, lower sUr target values must be achieved to at least “normal” levels, but preferably low to normal (≤0.30 mmol/l) [25, 27]. In order to prevent further attacks of gout, stable sUr target values of at least ≤0.36 mmol/l are required, but in the event of frequent or prolonged attacks, ≤0.30 mmol/l is preferable [23-25, 28].

Two main classes of drugs that reduce serum urate concentrations exist: xanthine oxidase inhibitors (XOi), such as allopurinol and febuxostat, and uricosuric drugs, such as benzbromarone and probenecid. Xanthine oxidase inhibitors work by inhibiting uric acid production, thereby reducing serum urate concentrations. Uricosuric drugs inhibit the

reabsorption of uric acid mediated by the URAT-1. Few comparative randomised studies have been carried out comparing the effectiveness of these drugs, Table 4 [27, 29-31].

Table 4. Effect of antihyperuricemic treatment on sUr in short-term studies.

Ref.	Effect on sUr	Allopurinol 200-300 mg	Benzbromarone 100-200 mg	Febuxostat 80-120 mg	Allopurinol 200-300 mg + probenecid 1,000 mg
27	≤0.30 mmol/l ≤0.36 mmol/l ΔsUr	30% 53% –34%	78% 100% ΔsUr –58%	-	-
30	≤0.30 mmol/l ≤0.36 mmol/l ΔsUr	13% 21% –33%	-	47-66% 53-62% –45-52%	-
31	≤0.30 mmol/l ≤0.36 mmol/l ΔsUr	25% 53% –36%	91% 97% –61%	-	86% 100% –54%

Legend: ΔsUr: change in serum urate concentration compared to baseline; sUr: serum urate concentration

Xanthine oxidase inhibitors

Allopurinol

Allopurinol is a purine-analogue XOi. Presently, allopurinol is the only available XOi. Allopurinol (100-900 mg daily) is rapidly metabolised into oxipurinol, a xanthine analogue that also inhibits xanthine oxidase, and is excreted in urine. A reduction in sUr concentrations to normal values can be achieved in 85% of cases using monotherapy of 300 mg allopurinol per day [24]. There are several studies with long-term data on the use of allopurinol in patients suffering from recurring attacks of gout, but they are of moderate quality [23, 32]. In a retrospective study, it appeared that 23% of patients had suffered a gout flare despite using allopurinol to reduce sUr to ≤0.36 mmol/l; 33% had an attack despite sUr level between 0.12-0.48 mmol/l), and 45% had an attack at sUr >0.48 mmol/l. The median allopurinol dosage was 300 mg/day, and only 34% achieved sUr levels ≤0.36 mmol/l [23].

Common AEs following treatment with allopurinol include hypersensitive skin reactions (exanthema in around 2% of cases) and occasionally short-term leukopenia, dizziness or nausea [33]. Severe AEs, such as systemic vasculitis, are possible in cases of renal insufficiency; therefore, the maintenance-dosing schedule should be adjusted in patients with impaired renal function [34]. When allopurinol is combined with azathioprine or mercaptopurine, the dosage of azathioprine or mercaptopurine should be reduced by 30% because of drug interaction. Mycophenolate mofetil may be considered for use in place of azathioprine in view of

a report that allopurinol has been safely combined with mycophenolate mofetil in five kidney transplant patients [35]. A rare but notorious AE of allopurinol is toxic epidermal necrolysis. Sporadic cases of neuritis or bone marrow suppression have also been observed.
As a prophylaxis for acute urate nephropathy among patients with chronic leukemia or malignant lymphoma undergoing aggressive chemotherapy, the advice is to start with high doses of allopurinol at least 3 days before the treatment with cytostatics and to ensure adequate diuresis. Rasburicase (recombinant uricase) may also be considered for this indication.

Febuxostat

Febuxostat 80-120 mg once daily is currently being developed for treatment of hyperuricemia in patients with gout. Unlike allopurinol, which is an analogue of the purine hypoxanthine, febuxostat has a non-purine-like structure. It is a selective inhibitor to xanthine oxidase. To date, the drug has shown efficacy in several studies [30, 36-38]. In a phase-II dose-response study the efficacy of 40 mg, 80 mg and 120 mg per day febuxostat was evaluated in 153 patients with hyperuricemia (baseline sUr ≥0.48 mmol/l) and gout [37]. Significantly more patients receiving febuxostat than placebo achieved an sUr level of ≤0.36 mmol/l) at each visit ($p<0.001$ for each comparison). The target sUr level (≤0.36 mmol/l) was achieved at study end in 0% of patients in the placebo group and 56%, 76% and 94% of patients in the 40 mg, 80 mg and 120 mg febuxostat groups, respectively. Gout attacks occurred with a similar frequency in the placebo (37%) and 40 mg febuxostat groups (35%), and with an increased frequency in the 80 mg and 120 mg febuxostat groups (43% and 55%, respectively). However, during colchicine prophylaxis, gout attacks occurred less frequently (8-13%).
In a phase-III trial comparing febuxostat with allopurinol in patients (n=762) with gout and hyperuricemia (sUr levels >0.48 mmol/l), significantly more patients febuxostat 80 mg and 120 mg reached sUr levels below 0.36 mmol/l than those receiving 300 mg allopurinol (80 mg febuxostat, 53%; 120 mg 62% and 300 mg allopurinol 21%; $p<0.001$ for each comparison). The overall incidence of gout attacks during weeks 9 through to week 52 was similar in all groups: 64% and 70% in the 80 mg and 120 mg febuxostat groups, and 64% of patients receiving allopurinol. Febuxostat also reduced the median tophus area by 83% and 66% in patients in the 80 mg and 120 mg groups compared with 50% in patients receiving allopurinol [30].
In terms of safety, to date, results from clinical trials have shown that febuxostat is well tolerated with a safety profile comparable to that of placebo and allopurinol [30, 36]. In a long-term phase-II extension study (n=116), the most common adverse events (AEs) were diarrhoea (which occurred in ten patients (9%) and was attributed to concomittant colchicine administration) and headache in five patients (4%). Five patients (4%) also had abnormal liver function tests, which were attributed to concomittant use of colchicine [36]. In the large phase-III comparator trial, the most frequent drug-related AEs were liver function abnormalities (4% in the 80 mg, 5% in the 120 mg febuxostat group, and 4% in the allopurinol group), diarrhoea (4%, 5%, and 4%, in each treatment group, respectively), joint-related signs and symptoms (<1%, 2%, and 2%), and

musculoskeletal/connective tissue signs (2%, 1%, and 2%). Most AEs were mild to moderate in intensity and the incidence of serious AEs was similar in all groups [30].
The drug profile of febuxostat also suggests a potential role in the presence of allopurinol intolerance or renal failure [39].

Uricosuric drugs

Benzbromarone

Benzbromarone is a long-acting, uricosuric drug. In the short term, sUr levels fall sharply with benzbromarone 100 mg/day, and decline to a lesser extent with 300 mg/day allopurinol [25-26]. There are 10-year data available from 200 patients on benzbromarone 80-125 mg/day in which sUr levels were reduced by an average 54%; the severity and incidence of gout attacks was reduced within 1 year by 75%; tophi disappeared in all cases within 18 months; and in 96% of patients, benzbromarone was well tolerated [40]. Among the 35% of patients who overproduce uric acid, with liberal hydration and alkalisation, acute events in the urinary tract occurred in only 3%, despite a history of urolithiasis in 33% [40]. Benzbromarone causes tophi to disappear more quickly than allopurinol; a fact that is explained by a stronger urate-lowering effect following treatment with benzbromarone 100-200 mg/day compared with allopurinol 300 mg/day [27]. However, benzbromarone has been shown to cause serious liver damage in some patients [41-42]. Consequently, liver function should be monitored during the first six months of treatment. With uricosurics, patients are advised to ensure diuresis of ≥2 l/day. In cases of severe renal insufficiency (glomerular filtration rate <20 ml/min), no therapeutic effect is to be expected from benzbromarone.
In terms of drug interactions, benzbromarone enhances the effect of coumarin derivatives by inhibiting the liver enzyme cytochrome P450 2C9 (CYP2C9) [43]. Theoretically, all drugs that are substrate of CYP2C9 (e.g. phenytoin), are prone to having an enhanced effect when combined with benzbromarone; however, there are no available data to verify this.
Benzbromarone is not available in the USA and the UK, and marketing was stopped in other countries in 2003 because of reports of serious liver damage in patients administered the drug. The drug is still available in the Netherlands, and can be prescribed in cases of intolerance or allergy to allopurinol.

Probenecid

Probenecid is an alternative URAT-1 inhibitor and is available in the US, Canada, France and Germany; it is not routinely available in the Netherlands and the UK. As far as we know, no long-term data are available on probenecid. A few studies have looked at combination therapy with both an XOi (i.e. allopurinol) and a uricosuric drug, such as probenecid or benzbromarone. It is a successful option in cases of severe tophaceous gout, or when allopurinol monotherapy is not effective [26].

Because of its renal action, probenecid increases the serum level of many drugs, such as thiazide diuretics, furosemide, beta-lactam antibiotics, indomethacin, and naproxen. Probenecid is usually dosed 500-1,000 mg twice daily.

Uricase analogues

Pegylated uricase is still at the research phase because it has been associated with antibody formation. Rasburicase is available in the European Union (EU) for the indication of tumour lysis syndrome. Rasburicase oxidises uric acid into allantoin, which is a highly hydrophilic molecule. Rasburicase has been used successfully in some cases with therapy-resistant gout [44-45]. Rasbruicase is not licensed for treatment of gout; therefore, local authorisation procedures are demanded.

Special considerations when treating gout

Antihyperuricemic therapy might provoke arthritis or induce an attack of gout. For safety reasons, antihyperuricemic therapy should only be given after a gout attack, preferably with protection from colchicine, which should be initiated several days to two weeks earlier (0.5 mg twice daily). With normal renal function, administration of allopurinol could be started at a dose of 100-300 mg once daily, probenecid 250 mg twice daily and benzbromarone 100 mg once daily. After two weeks, the dose can be increased if necessary. Standard maintenance doses are allopurinol 200-600 mg once daily, benzbromarone 100-200 mg once daily and probenecid 500-1,000 mg twice daily.

When frequent attacks of gout without joint damage or tophi are present in patients with intolerance or allergy to allopurinol and uricosurics, prophylaxis with colchicine at low doses can be prescribed, e.g. 0.5 mg once or twice daily in patients with good renal function. In exceptional cases, corticosteroids, or a combination of a uricosuricum and allopurinol, may be indicated for maintenance therapy. When a history of urolithiasis is present, adequate diuresis should be ensured and alkalisation should be considered, especially if a uricosuricum is prescribed.

Compliance is also a special consideration when supervising gout patients, and it is crucial to explain the dosing schedule and any potential side effects to the patient in order to prevent early withdrawal.

Conclusions

The limited information on drugs indicated for the treatment of gout, makes it difficult for physicians to compose informed treatment decisions. The current therapeutic strategy is often based on clinical experience. The value of lifestyle advice is limited in the prevention of gout, particularly with regard to restriction of alcohol, weight-loss in case of obesity, ensuring

adequate diuresis and adherence to a low-purine diet, as most patients are reluctant to make such changes. Therefore, the condition is often treated with pharmacological therapies.
Presently, oral colchicine and NSAIDs are first-line agents for systemic treatment of acute gout. In the absence of contra-indications, NSAIDs are a convenient and well-accepted option for treatment of acute gout. In case of tophaceous or recurrent gout, the use of urate-lowering drugs is recommended. Currently, allopurinol is the first choice antihyperuricemic drug. Many treatment options for gout have unwanted side effects, which highlights the importance of the development of new agents therapeutics for the treatment of gout.

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Chapter 2.2

Benzbromarone: an old drug with new perspectives; update of its clinical pharmacology

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Submitted

Abstract

Benzbromarone is an old, but very potent urate-lowering drug. New pharmacological data of clinical importance have become available, since its last drug profile was published in the early 1980s. Benzbromarone is predominantly metabolised by cytochrome P450 iso-enzyme 2C9 (CYP2C9) to the active metabolite 6-hydroxybenzbromarone, which is thought - because of its long half-life - to substantially account the uricosuric activity of benzbromarone.

Benzbromarone is a strong inhibitor of CYP2C9 leading to clinically important drug-drug interactions with acenocoumarol, phenprocoumon and warfarin, and theoretically with phenytoin, tolbutamide and other CYP2C9 substrates like some NSAIDs. Depending on the allele form of CYP2C9, the metabolism may be inhibited or activated.

Benzbromarone was tested in several clinical trials. However, most trials had poor quality: no randomisation, small number of patients, short duration, low dose of benzbromarone, or no clinical outcome. In general, benzbromarone 100 mg/day was found to be more effective (for control of serum urate) and better tolerated than allopurinol 300 mg/day or probenecid 1,000 mg/day.

Benzbromarone is well tolerated in general. Occasionally, gastro-intestinal complains and urolithiasis occur. In the last decade, benzbromarone was associated with a very rare, but life-threatening fulminant hepatitis. It was shown that mitochondrial toxicity might play a role in the mechanism and recently it was proposed from newly discovered glutathione adjunct metabolites, that a reactive quinone intermediate is formed by CYP2C9. In addition, since the adverse drug event is very rare, a genetic component (e.g. CYP2C9 allelic variants) and drug-drug interactions at CYP2C9 might play a role.

The hepatotoxicity risk led to a worldwide withdrawal of benzbromarone in 2003. However, because of requests of physicians, benzbromarone became available again in 2004 for treatment of gout patients who could not be treated with allopurinol. At present, benzbromarone has been incorporated in several guidelines and recommendations on the treatment of gout.

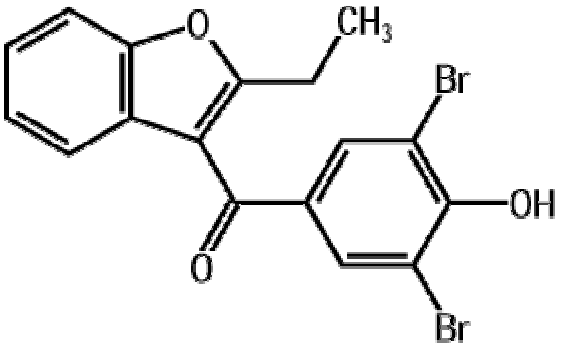
In conclusion, benzbromarone is an old, but very potent urate-lowering drug, and possesses some distinct, recently discovered pharmacological features, which are important for effective and safe use in treatment of gout.

Introduction

Benzbromarone is a uricosuric agent that is licensed in several countries for maintenance therapy in gout. In the international literature, the last drug profile on benzbromarone (3,5-dibromo-4-hydroxyphenyl-2-ethyl-3-benzofuranyl ketone, Figure 1) was published in the early 1980s [1-4]. Many reviews about antihyperuricemic drugs were recently published, but information on benzbromarone was limited [5-9]. After the worldwide withdrawal of benzbromarone in 2003, the interest in benzbromarone seemed to increase [10]. The reason for the withdrawal was - according to the information given by the manufacturer - the potential risk of fulminant hepatitis. Since the introduction of benzbromarone in the early 1970s, four cases of severe hepatitis have been published [11-14]. Additionally, eleven cases were reported by the company, but these are not available in the public domain [15]. Benzbromarone, however, seems well tolerated in general [16], and has been considered as the most potent oral antihyperuricemic drug. Because of requests of physicians, benzbromarone became available again in 2004 for treatment of gout patients who could not be treated with allopurinol. The use of benzbromarone has been advised in recent European and South African guidelines on treatment of gout [17-20].

In this review, new information regarding the pharmacology and therapeutic use of benzbromarone is presented. This information is of interest for rheumatologists and other health-care workers involved in the treatment of patients with gout, for utilising benzbromarone safely and effectively.

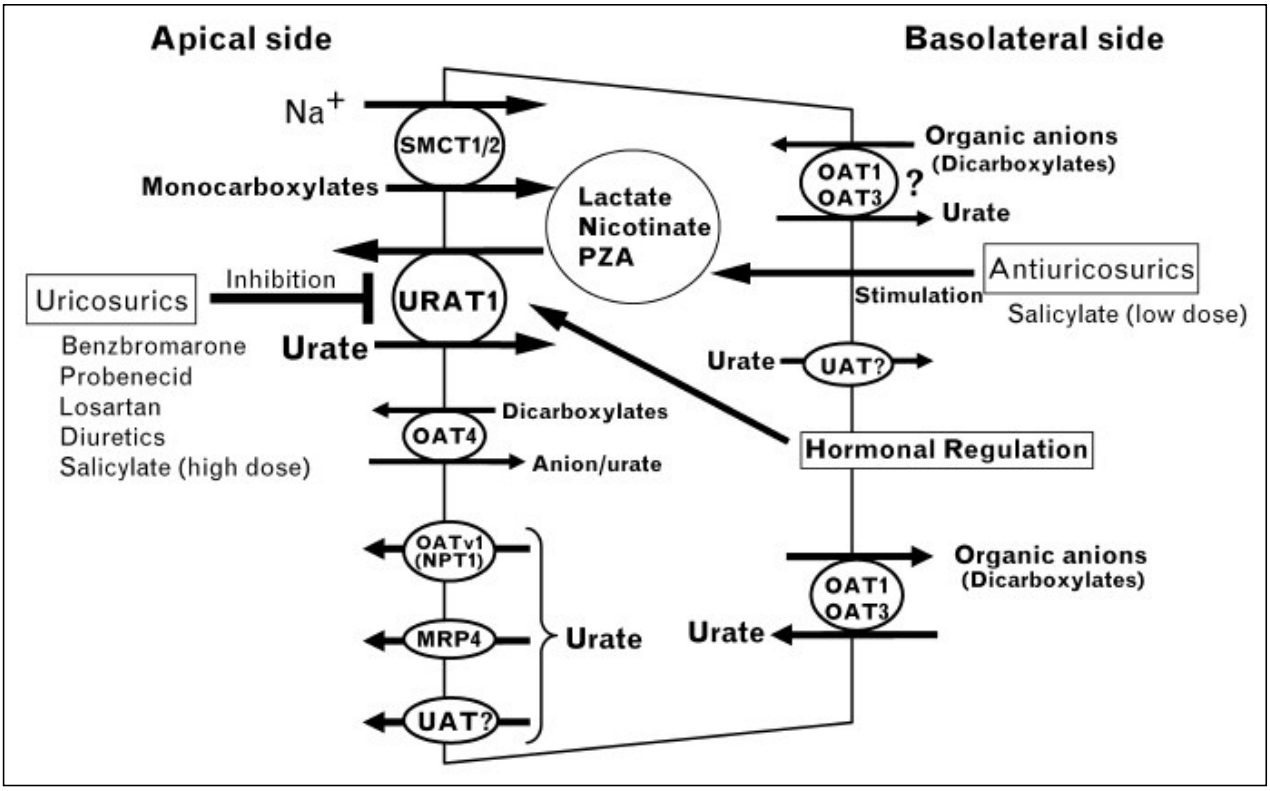
Figure 1. Chemical structure of benzbromarone



Urate homeostasis

Urate is the product of purine degradation in man. It is converted from xanthine and hypoxanthine by xanthine oxidase (XO). Xanthine oxidase and xanthine dehydrogenase are interconvertible forms of the same enzyme, known as xanthine oxidoreductase. It is a molybdenum-containing enzyme present in several organs, including liver and intestine. Urate is excreted by the kidneys for approximately two thirds and by the gut for one-third [21].

Figure 2. Model of indirect coupling of sodium and urate transport via URAT-1



Coupling of anions to sodium uptake along the luminal membrane and later exchange of the anions for urate by URAT-1 in the proximal tubulus. Drugs or agents with affinity for URAT-1 will be uricosuric when acting from the lumen, whereas they will be anti-uricosuric by driving the influx of urate when acting from the intracellular space, consequently regulating blood urate levels. The organic anions that are actively pumped into the proximal tubular cells from apical (or basolateral) sides or those produced in the cells should favour urate reabsorption, by leaving the cells in exchange with luminal urate. Transporters responsible for the urate excretion are basolateral OAT-1, OAT-3 and luminal OATv1/NPT1, MRP-4, OAT-4 and UAT. Two sodium-anion co-transporters that are expressed in the luminal membrane have been identified as SMCT1/2 (Slc5a8/Slc5a12) [24].

Hyperuricemia occurs when excretion of uric acid (urate) is lower than production (synthesis, cell turn over and dietary intake). This may be due to overproduction of urate, underexcretion of urate or a combination of both [22]. Overproduction of urate can be determined by measuring the total amount of urate excreted in urine per day. Overproduction of urate may occur in case of (treatment of) malignancies and purine-rich diet, such as red meat, fish, and beer. Alcoholic beverages may cause hyperuricemia by (1) increase of uric acid production by net adenosine triphosphate (ATP) degradation to adesine monophosphate (AMP), and (2) decreased urinary excretion because of dehydration and metabolic acidosis.

Underexcretion of urate can be determined by calculating the renal clearance of urate (about 6 ml/min per 1.73 m^2 in normal situation [23]). In 90% of gout patients, a diminished renal urate clearance is present [21]. Underexcretion of urate may be caused by genetic factors, clinical disorders (renal insufficiency), and endogenous (lactate, nicotinate, β-hydroxybutyrate, aceto-

acetate) or exogenous substances (cyclosporine A, tacrolimus, low dose salicylates, thiazides, pyrazinamide, ethambutol, beta-blockers) [21].

The proximal tubulus is the major site of urate handling by the kidney. Both reabsorption and excretion occur in this segment by several organic anion transporters (OATs, gene family *SLC22A*), with the net effect being the reabsorption of most of the filtered urate (Figure 2) [24-28]. OATs are expressed in the renal epithelial cells to regulate the excretion and reabsorption of endogenous and exogenous organic anions. These OATs are crucial components in the renal handling of drugs and their metabolites, and they are implicated in various clinically important drug interactions, and their adverse reactions. In 2002, the predominant urate re-uptake transporter in the proximal tubulus was identified as urate transporter-1 (URAT-1) (*SLC22A12*) [28]. Recently, it was shown that polymorphisms in the N-terminus of the URAT-1 gene were significantly associated with reduced renal uric acid excretion [29]. Thiazide-induced hyperuricemia is associated with modification of urate transport by OAT-4 [30].

When hyperuricemia is present for a longer period, it can manifest with symptoms caused by deposition of monosodium urate crystals, such as gout attacks, tophi, urate urolithiasis and urate nephropathy. Other factors influencing deposition of urate crystals include temperature, pH, concentration of cations, level of articular dehydration, and the presence of such nucleating agents as non-aggregated proteoglycans, insoluble collagens, and chondroitin sulphate. Drugs that lower serum urate, include xanthine oxidase (XO) inhibitors (allopurinol, febuxostat), uricosurics (benzbromarone, probenecid, sulfinpyrazone) and uricolytics (pegylated-uricase, rasburicase).

Uricostatics

Xanthine oxidase (XO) inhibitors prevent the formation of urate and hydrogen peroxide from xanthine and hypoxanthine by inhibiting the enzyme XO. Consequently, concomitant effects of XO-inhibitors are (1) increase of serum and urinary xanthine concentrations, which may cause xanthinuria, and (2) increase of serum concentrations of drugs metabolised by XO, such as mercaptopurines (azathioprine, 6-mercaptopurine) and didanosine, which may lead to toxicity. Inhibitors of xanthine oxidase used in clinical practice or tested in clinical studies include allopurinol (licensed), febuxostat, oxipurinol, and Y-700 [32].

Uricosurics

Uricosurics prevent the re-uptake of urate in the proximal tubulus predominantly by inhibiting the URAT-1 transporter resulting in an increased renal urate clearance [27]. Uricosurics can also modify other OATs [25]. Some drug-drug interactions of uricosurics can be explained by the latter, such as the increase of methotrexate blood levels by probenecid [31]. Efficacy of uricosurics is diminished in renal insufficiency. Licensed uricosuric drugs include benzbromarone, probenecid and sulfinpyrazone. Some drugs have a (modest) concomitant

uricosuric effect, such as losartan, amlodipine, fenofibrate, tienilic acid, and high-dose salicylates, but these drugs are not primarily used for treatment of gout [33-35].

Uricolytics

Uricases represents a group of enzymes from non-human origin, which can convert urate to allantoin and hydrogen peroxide. Uricolytics used in clinical practice or tested in clinical studies include uricase, rasburicase, and pegylated uricase (pegloticase) [36].

Characteristics of benzbromarone

Clinical pharmacokinetics, pharmacodynamics and metabolism

After oral intake of a single dose of 100 mg benzbromarone, about 50% is absorbed [37]. Following absorption, benzbromarone undergoes extensive conversion in the liver, mainly to two active metabolites: 1'-hydroxybenzbromarone and 6-hydroxybenzbromarone [38-40]. About 75% of the absorbed drug is converted to 6-hydroxybenzbromarone, predominantly by cytochrome P450 2C9 (CYP2C9) [41-42]. CYP2C19 is a minor benzbromarone-converting enzyme [43].

In addition, several minor metabolites are identified in plasma and urine [38-46]. Previously, it was assumed that benzbromarone was predominantly debrominated [1], but this is not correct as proven by mass-spectrometry analysis of patient serum samples [38-44]. Benzbromarone is largely bound to proteins in serum (99%). Benzbromarone and metabolites are predominantly excreted in the bile; 6% of benzbromarone is excreted in urine as glucuronidated conjugates [47].

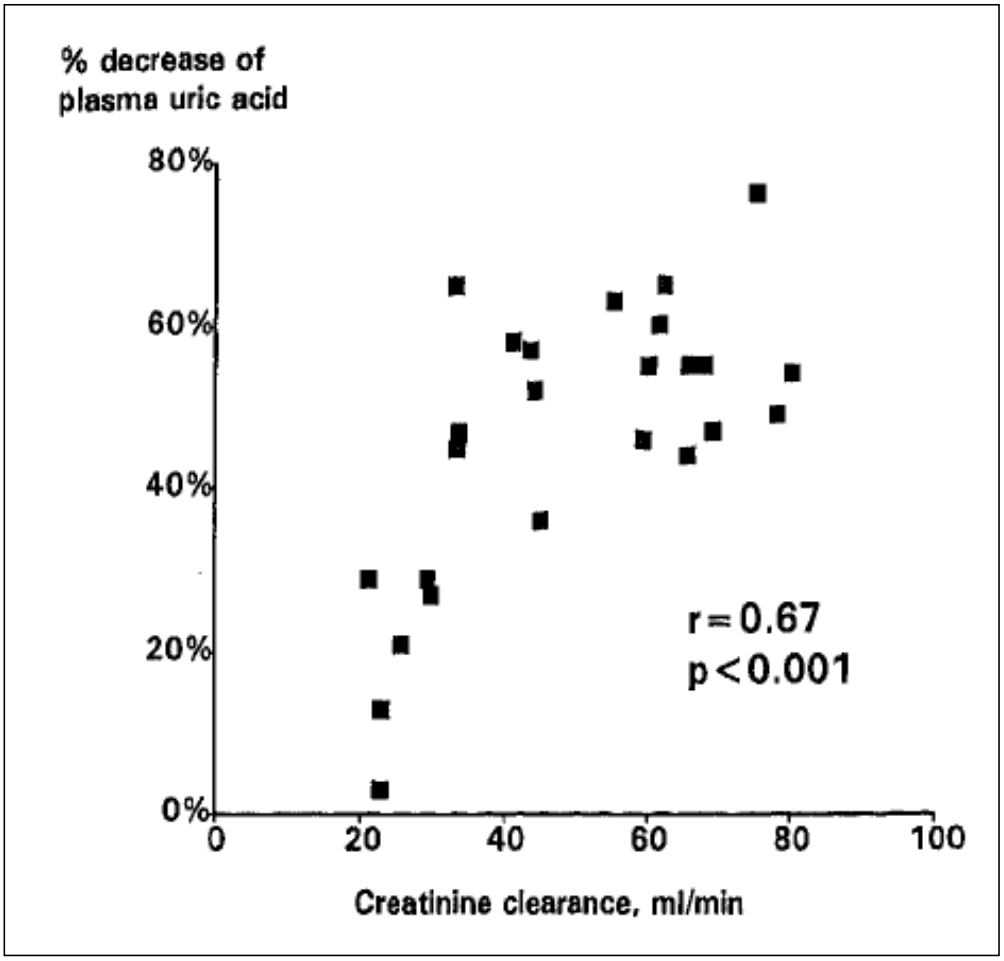
In a study of 11 healthy volunteers (10 "normal" metabolisers), the following elimination half life ($t_{½}$) values were found: benzbromarone 3.3 [± 1.1] h (mean [± standard deviation]), 1'-hydroxy-benzbromarone 20.1 [± 9.8] h and 6-hydroxybenzbromarone 17.2 [± 5.2] h [48]. In another study of 11 healthy volunteers (9 "normal" metabolisers), $t_{½}$ values were: benzbromarone 5.4 [± 1.9] h; 1'-hydroxybenzbromarone 18.5 [± 16.3] h and 6-hydroxybenzbromarone 23.3 [± 24.8] h [49].

URAT-1 mediated urate uptake is inhibited by 6-hydroxybenzbromarone *in vitro* in a dose-related manner, with a half maximal inhibitory concentration (IC_{50}) of 0.20 [± 0.06] µM, whereas the IC_{50} of benzbromarone was found to be 0.035 [± 0.003] µM [45]. It is suggested that, given the pharmacokinetic profile of 6-hydroxybenzbromarone, this metabolite particularly contributes to the duration of the uricosuric effect [45].

In patients with compensated liver cirrhosis Child A and B, pharmacokinetics and efficacy of benzbromarone after a single dose of 100 mg was investigated by Walter-Sack *et al*. [50]. They did not observe any important differences compared to values obtained in healthy subjects, and suggested that dose adjustment was not necessary.

In patients with renal impairment, efficacy of uricosurics is generally reduced because of a lower drug concentration at the site of action. It is shown that benzbromarone is effective in patients with calculated creatinine clearances (cCrCl) of 20-80 ml/min per 1.73 m^2 [51].
In addition, benzbromarone 100 mg was effective in renal transplant patients taking cyclosporin A, and a relation between antihyperuricemic efficacy and renal function was observed, Figure 3 [52]. When efficacy of benzbromarone is insufficient in patients with renal function impairment, increase of dosage might be effective, especially when cCrCl is 20-40 ml/min per 1.73 m^2. Otherwise, combination therapy with a XO-inhibitor is useful [53].

Figure 3: Effectiveness of benzbromarone in renal function impairment



Relative decrease (in percent of initial values) of plasma urate in function of calculated creatinine clearance in patients on cyclosporine A taking benzbromarone 100 mg daily [52].

Drug-drug interactions

Benzbromarone is a potent inhibitor of CYP2C9 with a K_i of 20 nM *in vitro* [54-57]. The inhibition profile of 6-hydroxybenzbromarone has not been studied. Theoretically, several clinically relevant interactions could occur with drugs predominantly metabolised by CYP2C9: coumarins (acenocoumarol, phenprocoumon, and warfarin), some angiotensin-II antagonists (losartan,

irbesartan), fluvastatin, glipizide, phenytoin, several NSAIDs (diclofenac, ibuprofen, and naproxen), sulfamethoxazole, tamoxifen, tolbutamide, and torsemide [58-59]. Especially the interactions with low therapeutic index substrates - coumarins, phenytoin, and tolbutamide - require attention. However, only a clinical interactive effect of benzbromarone with warfarin has been reported in literature [54-60].

Substrate-specific differences on CYP2C9 mediated metabolism are described for benzbromarone: activation of CYP2C9 mediated naproxen *O*-demethylase activity occurred (to a maximum of 250% at approximately 1 µM), whereas potent inhibition of diclofenac ’4-hydroxylation was observed ($IC_{50,\ apparent}$ at 0.04 µM) [57].

Furthermore, benzbromarone inhibits reabsorption of oxipurinol (the active metabolite of allopurinol) by the URAT-1 transporter. Consequently, the effect of allopurinol therapy is diminished due to decreased oxipurinol concentrations in the body [61-64]. This interactive effect has also been described for allopurinol with probenecid [63].

The antihyperuricemic activity of benzbromarone is largely diminished when pyrazinamide is co-administered, presumably because the active metabolite pyrazinoate blocks the excretion of urate in the proximal tubulus, which cannot be fully compensated by the inhibition of URAT-1 by benzbromarone [65]. The same interactive effect has been described for salicylates (>300 mg dose) with benzbromarone [1, 3].

Pharmacogenetics

Two types of slow benzbromarone eliminators have been identified [48-49, 66-67]. The first one, “type 1”, eliminated benzbromarone as well as the metabolites 1’-hydroxybenzbromarone and 6-hydroxybenzbromarone slowly [48]. The “type 2” eliminator showed a delayed elimination of benzbromarone and 1’-hydroxybenzbromarone, but a reduced formation of 6-hydroxy-benzbromarone [49]. The type 2 poor elimination profile is consistent with a 64% reduction of the AUC ratio of 6-hydroxybenzbromarone to benzbromarone in one patient with CYP2C9*3/*3 genotype compared to wild-type patients (CYP2C9*1/*1) [68]. Patients with CYP2C9*1/*3 did not have important alterations in this study.

In another study with CYP2C9*3 genotype patients, it was found that benzbromarone inhibited the CYP2C9-mediated ’4-hydroxylation of flurbiprofen in CYP2C9*1, but unexpectedly activated ’4-hydroxylation in the CYP2C9*3 genotype [69]. The same pattern was shown with naproxen and desmethylnaproxen [70].

Adverse effects, contra-indications and precautions

Most clinical trials of benzbromarone have reported little or no adverse reactions. Metabolism of benzbromarone was studied in two persons intoxicated (suicidally) with high doses of benzbromarone [46]. Information on incidence of adverse effects is available from several large observational studies (Table) and from a 10-year follow-up study [16]. Discontinuation of treatment due to intolerance is usually because of diarrhoea, and has been reported in 3.5% of

patients [16]. Another common side effect of benzbromarone is the occurrence of urolithiasis related to formation of urate stones (3%) [16]. The risk of urolithiasis is higher when the urinary urate concentration increases, which is inherent to the working mechanism of benzbromarone, or in presence of renal function impairment. Patients with a urinary urate excretion (uUr) >4.2 mmol/day are (relatively) contra-indicated for using benzbromarone [90]. Excretion of urate in urine can be diminished by applying a diet low in purines or by treatment with allopurinol. Otherwise, the risk of urate urolithiasis might be lowered by intake of fluids (>2 l/day), use of diuretics or increase of a low urine pH [90].

Acute gout attacks are common side effects during the initiation of any antihyperuricemic therapy due to urate mobilisation, and have been reported with benzbromarone therapy [16]. Prevention of acute gout attacks evoked by urate lowering therapy might be accomplished by a stepwise increase of benzbromarone dosage, and by adding colchicine or NSAIDs until serum urate levels are stabilised. Other adverse reactions such as temporary impotence, allergic conjunctivitis and severe skin rash have also been reported, but only in sporadic cases [2, 16].

Concerns on the safety of benzbromarone focus on cases of severe hepatotoxicity diagnosed several months after start of benzbromarone [11-14]. Results from clinical trials showed about 0.5% of patients with “elevated liver enzymes”, but no jaundice [90]. It must be taken into account that up to 2.5% of healthy individuals will have an abnormal test result of a given liver chemistry test, based on the definition of the upper limit of the normal range. No complication was found in eight patients with liver cirrhosis receiving benzbromarone [50]. However, given the infrequent and idiosyncratic nature of hepatotoxicity, tolerance in this small group is not unexpected. Causes of benzbromarone hepatotoxicity might exist in CYP2C9 allelic variants (formation of toxic metabolites, diminished elimination) or in CYP2C9 interactions with concomitant drugs known to cause hepatotoxicity, such as diclofenac. No information about the toxicity of the metabolites of benzbromarone, such as 1’-hydroxybenzbromarone and 6-hydroxy-benzbromarone is available. It is advised to monitor liver function before and at regular intervals during benzbromarone therapy, at least during the first six months; benzbromarone therapy must be stopped when elevated liver functions are present [90-91].

In *in vitro* studies, benzbromarone, benzarone and amiodarone - structural analogues - were shown to inhibit the mitochondrial respiratory chain and β-oxidation and are uncouplers of oxidative phosphorylation. Furthermore, they can induce reactive oxygen species (ROS) production and mitochondrial swelling, which may lead to apoptosis and necrosis of cells [93]. Furthermore, a series of toxicological studies demonstrated proliferation of peroxisomes in the liver of the rat dosed with benzbromarone [94-96]. This is a mechanism associated with carcinogenesis, although the same effect could not be demonstrated in human hepatocytes. The peroxisome proliferation property of benzbromarone in rat hepatocytes was further investigated. Benzbromarone is a ligand of PPAR-α but not PPAR-γ. PPAR-γ is associated with apoptosis and is thought to be the mechanism of troglitazone-induced fulminant hepatitis [97].

Table. Clinical trials of benzbromarone in hyperuricemic or gouty patients

Dosage (mg/day)	Treatment comparison	Trial type	No. of patients	Trial period	Serum urate reduction (mean) [a]	Gout attacks reduction	Ref.
100	Baseline	RCT	20	7 days	46% vs 0%	NA	[71]
25-100	Baseline	CT	55	2-6 years	48% vs 0%	NA	[72]
100-200	Baseline [b]	CT	6	3 weeks	42% vs 0%	NA	[73]
100	Baseline [b]	CT	43	24 weeks	54% vs 0%	NA	[74]
50-100	Baseline	CT	2220	8 weeks	26% vs 0%	NA	[75]
40-80	Baseline	CT	408	42 weeks	34% vs. 0%	36% vs. 0%	[76]
50-100	Baseline	CT	6	1 year	25% vs. 0%	54% vs. 0%	[77]
100	Allopurinol 200 mg/day	RCT	20	7 days	34% vs. 37% (p>0.05)	NA	[78]
50	Allopurinol 300 mg/day	CCT	28	7 days	45% vs. 38%	NA	[79]
100	Allopurinol 300 mg/day	CCT	6	7 days	51% vs. 14%	NA	[80]
100	Allopurinol 300 mg/day	CCT	86	1 year	58% vs. 36%	NA	[81]
100-200	Allopurinol 300 mg/day [b]	RCT	36	9-24 months	56% vs. 33#	NS	[51]
100	Allopurinol 300 mg/day	CCT	14	4 weeks	58% vs. 45%	NA	[82]
100	Probenecid 1,000 mg/day	RCT	6	1 week	51% vs. 23%	NA	[80]
50	Probenecid 500-1,000 mg/day	RCT	74	12 weeks	40% vs. 32%	NA	[83]
Comb [c]	Allopurinol 300 mg/day	CCT	67	1 week	36% vs. 40%	NA	[84]
Comb [c]	Allopurinol 100 mg/day	RCT	12	4 weeks	35% vs. 21%	NA	[85]
Comb [c]	Benzbromarone 20 mg/day	RCT	12	4 weeks	35% vs. 20%	NA	[85]
Comb [c]	Allopurinol 300 mg/day	RCT	80	36 weeks	40% vs. 40%	NA	[86]
Comb [c]	Allopurinol 300 mg/day	RCT	60	24 weeks	27% vs. 20%	NA	[87]
Comb [c]	Allopurinol 300 mg/day	CCT	94	4 weeks	26% vs. 40%	NA	[88]

Abbreviations: CT: clinical trial (within person comparison); CCT: controlled clinical trial; NA: not assessed; NS: non-significant difference; RCT: randomised controlled trial.

[a] Order of comparison is “effect of benzbromarone” vs. “effect of drug in comparison”, followed by p-value in brackets; p value between all serum urate reductions were significant (p<0.05) unless otherwise stated.

[b] Trials conducted in patients with renal impairment, calculated creatinine clearance (cCrCl) 20-80 ml/min.

[c] Allopurinol 100 mg and benzbromarone 20 mg.

Clinical efficacy

Preferably, the efficacy of antihyperuricemic drugs should be tested on prevention of gouty arthritis and joint damage in randomised controlled trials (RCT). Very few RCTs of good quality have been done with antihyperuricemic drugs, and none with benzbromarone [98-99]. On the other hand, some comparative clinical trials provide useful information about the antihyperuricemic efficacy of several drugs and dosages. Since frequency of gouty attacks and diminishing of tophi are related to serum urate levels, this parameter is considered a next best measure for determination of clinical success of antihyperuricemic drugs.

Benzbromarone is compared with other urate lowering drugs in dosages of 20-200 mg daily in a number of trials (Table), trials were identified from Medline and Embase using “benzbromarone” and “clinical trial”, and from a recent review [15]. Most trials have deficits regarding number of patients, treatment duration or benzbromarone dosage. Results of relative sUr decrease with benzbromarone ranges from 25 to 58%. Differences in effectiveness can occur because of variation in dosage, treatment duration, and renal function. For instance, Ferber *et al.* used a dosage of 100 mg in just 330 of 1,984 patients [75]. Usual maintenance dosage of benzbromarone in clinical practice is 100 mg, generally demonstrating around 50% decrease of serum urate, and showing significant better results than allopurinol 300 mg daily [81-82].

Theoretically, a difference in time to reach (initial) steady state of serum urate levels - dependent on serum elimination half-life of urate (~3-5*$t_{½}$) - exists between uricosuric drugs and xanthine oxidase inhibitors,. Steady state is more rapidly reached in case of better renal urate clearance, thus when using uricosurics. In normal patients urate $t_{½}$ = 3.5 days. In underexcretor-type gout patients urate $t_{½}$ can be prolonged to as long as 12 days, whereas it can be diminished to as short as 12 hours by using benzbromarone. Thus, when comparing uricosurics with xanthine oxidase inhibitors, allopurinol results can only be properly evaluated after treatment of 1-2 months.

Conclusion

Benzbromarone is an old, but very potent urate-lowering drug, and possesses some distinct, recently discovered pharmacological features, which are important for effective and safe use in treatment of gout. Although benzbromarone is on the market for several decades, its place in treatment of gout compared to allopurinol is unclear, because of insufficient trials of good quality. The toxicity of benzbromarone is generally limited, but serious benzbromarone-induced hepatic failure is reported in rare cases. The underlying mechanism has not yet been fully explained, but formation of reactive metabolites by CYP2C9 resulting in mitochondrial toxicity, and CYP2C9 polymorphisms might play a role. Important drug-drug interactions may occur with CYP2C9-metabolised drugs, but clinical data are lacking for most drugs.

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